Patricia Abreu (Universidade Federal São Paulo - Brazil):
This conference will clarify key points in the treatment of anemia. I am especially optimistic about HIF-PHI and iron metabolism. Great job everyone Thanks for the invitation.

Afsar Baris (Suleyman Demirel University):
Group 1: Therapeutic use of HIF-PHIs vs. current therapies in anemia management: CKD patients not on dialysis treatment

Comment 1: Are there any patient groups that HIF-PHIs are absolutely contraindicated in CKD patients not on dialysis treatment.

Comment 2: Which patients prefer ESA and which patients prefer HIF-PHIs. Should there be any classification?

Comment 3: Are there any conditions which ESA and HIF-PHIs should be used together?

Comment 4: Are there any cost differences between ESAs and HIF-PHIs in these patient group?

Group 2: Therapeutic use of HIF-PHIs vs. current therapies in anemia management: CKD patients treated with dialysis (patients incident and prevalent to dialysis)

Comment 1: Are there any patient groups that HIF-PHIs are absolutely contraindicated in CKD patients not on dialysis treatment.

Comment 2: Which patients prefer ESA and which patients prefer HIF-PHIs. Should there be any classification?
Comment 3: Are there any conditions which ESA and HIF-PHIs should be used together?

Comment 4: Are there any cost differences between ESAs and HIF-PHIs in these patient group?

Comment 5: Are there any differences between dialysis complications (cramps, dialysis hypotension etc.) between ESas and HIF-PHIs

Group 3: Safety profile of HIF-PHIs in CKD anemia management

Comment 1: Are there any differences regarding oncologic outcomes between ESAs and HIF-PHIs

Comment 2: Are there any differences regarding access failure between ESAs and HIF-PHIs

Group 4: Pathophysiology of HIF-PHIs and pleiotropic effects beyond hemoglobin

Comment 1: What are the effects of HIF-PHIs on renal fibrosis, carbohydrate and lipid metabolism

Tadao Akizawa (Showa University School of Medicine):
Good. No particular additional comments.

Mona Alrukhaimi (ISN, Emirate Nephrology Society):
It looks great and cover all the aspects.

Jodie Babitt (Massachusetts General Hospital, Harvard Medical School):
Group 1, points 4, 6, 7 (also relevant for group 2, point 4, 7, 8). Suggest to word more neutrally, i.e. is there evidence of benefit or evidence of harm; comparative advantage or disadvantage, etc. Also, not clear that HIF-PHI will fully replace iron/ESA. Iron may still be needed.

Group 2: Should there be distinction for HD vs PD?

Group 3, point 2. Other populations to consider: patients with history of malignancy, pulmonary arterial hypertension

Group 3, point 6. What would be the rationale for using both ESA and HIF-PHI?
Group 4, point 8: Modality of ESA dosing should also be considered (IV vs SQ). Does SQ ESA dosing mirror more closely HIF-PHI in regards to EPO levels?

Jonathan Barratt (University of Leicester):
Very comprehensive scope for work which I believe cover all the major controversial areas in anaemic management in kidney disease- no suggested changes to the scope from my perspective.

Sunil Bhandari (Hull University Teaching Hospitals NHS Trust):
Having read the comprehensive document - I may have missed it but one key question related to HIF stabilizers is how will patients be iron repleted in both dialysis and non dialysis? - in dialysis would be want to use oral iron and increase the tablet burden and potential increased risk of impacting other medications, not to mention compliance. - what regime of IV iron would we now consider given the PIVOTAL trial with ESA use if we were to switch to a HIF stabilizer? would we consider reduced dosing. In non dialysis - currently clinical practice is varied around the world of IV versus oral repletion. As detailed, safety of HIF stabilizers remains to be fully evaluated and the Hb target range which will lead to optimal outcomes. Finally I am not sure if one group in which HIF stabilisers might be beneficial is been looked at - namely those with inflammation.

Aleix Cases (Hospital Clinic Barcelona, Spain):
Group 1: Therapeutic use of HIF-PHIs vs. current therapies in anemia management: CKD patients not on dialysis treatment

3. What is the appropriate dose for HIF-PHIs and how should dosing be adjusted (based on what parameters)? How do we manage a patient converting from the use of ESA to HIF-PHI?

COMMENT Concerns on rapid increases in Hb during the correction phase (as seen in some studies with roxadustat). Guidelines say that the rate of Hb increase should not be > 2 g/dl/month with ESA. Does this apply to HIF-PHIs? Is safe the faster increases in Hb seen with some HIF-PHI? We need conversion tables from ESAs to HIF-PHI.

5. What is the current evidence-based data surrounding differences between HIFPHI agents in patients with CKD not on dialysis?

COMMENT Clinically relevant differences between them according to differences in half-live, dose interval or PHI selectivity?
6. Are there particular advantages to the use of oral HIF-PHIs in the non-dialysis CKD population as compared to the dialysis population? Cost-savings, resource utilization, or COVID-19 pandemic-related considerations?

Not only advantages but also concerns higher pill burden, compliance (oral drug) or interactions with other drugs (especially those frequent in our population (phosphate binders, etc)

7. What is the role of iron and EPO in the era of HIF-PHIs for patients with CKD not on dialysis treatment? What is the comparative advantage of HIF-PHIs relative to iron and EPO

COMMENT: Ferritin and TSAT targets for iron repletion different with HIF-PHI vs ESA ? If patients require lower iron doses this may reduce the risk of iron overload, especially in the liver

Group 2: Therapeutic use of HIF-PHIs vs. current therapies in anemia management: CKD patients treated with dialysis (patients incident and prevalent to dialysis)

1. What is the efficacy of HIF-PHIs in the treatment of anemia in patients on dialysis therapy and the mean hemoglobin change that we can expect under standard treatment? Does this differ from patients with CKD not on dialysis treatment?

COMMENT Same effect or lower effect requiring higher doses of HIF-PHI in HD patients vs ND-CKD patients as occurs with ESA ?

3. What is the appropriate dose for HIF-PHIs and how should dosing be adjusted (based on what parameters)? How do we manage a patient converting from the use of ESA to HIF-PHI?

Same as previous

4. Is there any evidence that the use of HIF-PHIs slow down the progression of CKD, improve cardiovascular endpoints (MACE) or physical function and healthrelated quality of life compared with iron/ESAs? Are there any differences between the incident vs prevalent dialysis populations?

Slow down the progression of CKD not applicable in dialysis patients
7. Are there advantages to HIF-PHI use in patients who are hyporesponsive to ESA or iron? Cost-savings, resource utilization, or COVID-19 pandemic-related considerations? Do HIF-PHIs reduce iron requirements among patients receiving dialysis?

We need data on really inflamed and hyporesponsive patients from RCT or especially real world data. Data from RCT are not necessarily applicable to real world patients (more comorbidities, more inflamed and with real ESA resistance, not relying on CRP)

8. Are there subgroups for which HIF-PHIs might be particularly beneficial, such as patients receiving home dialysis therapies?

Including PD patients

Group 3: Safety profile of HIF-PHIs in CKD anemia management

1. What are the currently available safety data surrounding use of HIF-PHIs in different populations: patients not on dialysis; patients who are incident or prevalent to dialysis? Is there any evidence that safety differs by level of GFR or inflammatory states?

The results of the vadadustat study in ND-CKD patients with regional differences according to Hb target pose a new question. The beneficial or negative effect according to target Hb or baseline ESA dose. Since the non inferiority occurred in the America’s region but not in Europe with more liberal Hb targets, the initial explanation can be that targeting higher Hb doses with vadadustat can be dangerous. However, we must account for differences in ESA doses between America’s and Europe. Is non inferiority seen only among those requiring higher ESA doses, but not in those who respond better to ESA ?

2. Does the use of HIF-PHIs apply to anemia of CKD in kidney transplant populations with low eGFR and anemia? Pediatric populations? Older adults? Patients with underlying liver disease, polycystic kidney disease, or diabetic retinopathy? Immunosuppressed patients (e.g., due to underlying GN)? Patients with AKI?

In kidney transplant patients are there evidences of drug interactions with immunosupresive drugs ?

3. What parameters should be monitored during the treatment of anemia when using HIF-PHIs? Are there novel biomarkers or testing that should be made available to ensure safety? What toxicities should be monitored for?
Other adverse events of interest in nephrology with respect to HIF-PHI can be arteriovenous fistula thrombosis or stenosis. Venous thrombotic events (DVT or VTE). Macular degeneration or diabetic retinopathy. Cyst progression in PKD or in acquired cystic disease in dialysis patients. Higher incidence of pulmonary hypertension

5. What long-term post-marketing data may be needed given the numerous potential actions of HIF-PHIs that may not be intended?

Theoretical risks that may be of concern (e.g., oncologic)? Already mentioned in point 3

6. Are there drug-drug interactions that should be considered with the use of HIF-PHIs?

Do we have safety data on patients who are simultaneously on ESA and HIF-PHI therapies? High pill burden common in these patients can be an issue with respect to drug-drug interactions, tolerability and/or compliance Possible interactions with SGLT2 inhibitors (used for nephroprotection) but with common mechanisms of action. (Packer M Mechanisms Leading to Differential Hypoxia-Inducible Factor Signaling in the Diabetic Kidney: Modulation by SGLT2 Inhibitors and Hypoxia Mimetics. AJKD 2021; Am J Kidney Dis. 77(2):280-286)

Group 4: Pathophysiology of HIF-PHIs and pleiotropic effects beyond hemoglobin

1. What is the physiologic role of HIF-PHIs and their interaction with EPO and iron and effects on their metabolism?

Different roles of HIF-1alfa and HIF-2alfa on kidney fibrosis, inflammation, EPO production. Different activation of HIF-1alfa and HIF-2alfa according to differences in PHI inhibition selectivity. Off-target effects on other PH or other enzymes that require oxoglutarate as cofactor?

3. What are the theoretical off-target effects that warrant considerations as we begin to assess the impact of HIF-PHIs on major adverse cardiovascular events as mediated by effects on BP, cholesterol, etc.?

Do these benefits seem to be agent specific or common across the HIF-PHI class? Do these benefits are clinically relevant in the CKD and dialysis subset of patients (e.g. given the limited beneficial effects of statins in advanced CKD and HD patients

4. Do HIF-PHIs affect BP or dyslipidemia differentially among patients not on dialysis therapy or on dialysis?
Electrolytes or acid-base disturbances? Effect on serum K and risk of hyperkalemia? Some hints. Effects on bone?

**Rolando Claure-Del Granado (Hospital Obrero No 2 - CNS):**
You should include some patient centered outcomes like: physical functioning and quality of life (QOL), mental and emotional QOL, social QOL, fatigue, vitality, and energy levels, and global well-being and QOL.

**Lucia Del Vecchio (Azienda Socio Sanitaria Territoriale Lariana):**
Pg 1: clinical trials have indicated that ESAs, when used to target the low-normal… please correct with high-normal

Pg 1, last sentence. The explanation of the PIVOTAL trial is not precise. I suggest dividing the sentence in two. First that there were concerns on iv iron therapy in respect of increased mortality on those having high serum ferritin and that the PIVOTAL trial demonstrated that proactive IV iron therapy targeting ferritin levels till 700 ng/ml reduces the risk of cardiovascular events in comparison to a reactive treatment targeting lower ferritin levels in a population of incident HD patients with low signs of inflammation. A secondary analysis of the PIVOTAL showed the proactive therapy did not increase the risk of infections

Pg 2, line 7: The HIF system has several functions. “coordinates response to hypoxia, also stimulating erythropoietin synthesis.

Pg 2, line 9: HIF is also linked to iron metabolism by promoting iron absorption and utilisation (even if with a yet incompletely understood manner). It is known that….. (these concepts should be separated)

Pg 2, line 14: prolyl hydroxylation is inhibited and thus HIF degradation.

Pg 2, HIF-PHIs are approved also in Chile

Pg 2, last sentence. Pleiotropic effects: some of them are beneficial in theory; it is unknown if this translates into a benefit from the clinical point of view. The same for possible negative effects

Pg 3, last sentence: I would add also how HIF-PHI will be used in respect to ESA therapy

**Tilman Drueke (Inserm U1018, CESP, Paul Brousse hospital, Villejuif/Paris):**
For me the outline of the scope of this second controversies conference on anemia management in CKD is OK.

Main comments

1. The reference list should contain the second NEJM 2019 paper by Chen et al and in addition all recently published phase 3 trials on HIF-PHIs.

2. Group 2 should also address the issue of probably different indications of HIP-PHI treatment between HD and PD patients.

3. Group 4 should discuss the claim that HIF-PHIs are more efficacious than ESAs in patients with inflammation.

Minor remarks

P1 para 3. « … and actually confer worsen cardiovascular outcomes … ». Please check wording.

P2 para 2. I would say « in the kidneys and the liver » instead of « in the liver and kidneys » since in physiological conditions the kidneys are the main provider of Epo.

P2 para 3 L1. Why « thus » ?

P2 para 3 L3. I would say « and upregulates numerous genes including the following ».

P2 para 3 L9. I suggest to replace « hepcidin antimicrobial peptide transcription, inhibiting hepcidin production » by « hepcidin production ». The fact that hepcidin also has antimicrobial activity would otherwise need to be explained in more detail.

P2 para 4. For the plural of PHI please use either « PHIs » or « PHI », not alternatively the two of them. P6 point 4. « slows » and « and improves ».

Michele Eisenga (University Medical Center Groningen):
Wonderful Scope of Work which was a delight to read and which highlights the crucial questions that need to be answered regarding HIF-PHI use in CKD patients. However, a topic that is currently not stated concerns the interaction between ESA and HIF-PHI with fibroblast growth factor 23 (FGF23). In my opinion, this topic needs to be discussed in detail, with at least one specific bullet point in Group 4 and possibly also in Group 3.
Previously, it has been established in both the non-CKD and CKD setting and after kidney transplantation that high endogenous EPO levels as well as administration of exogenous EPO results in increased production with concomitantly increased cleavage of FGF23, resulting in a massive increase in C-terminal FGF23 fragments (Hanudel MR, Eisenga MF et al. Nephrol Dial Transplant 2019; Eisenga MF et al. J Am Heart Assoc 2019; Eisenga MF et al. J Clin Med 2020), elevated levels of which are known to be an important risk factor for ESRD and death in CKD patients (Isakova T et al. JAMA 2011). HIF-PHI administration leads to the same pattern of increased production and cleavage of FGF23, although peak levels tend to be lower (Flamme I et al. Plos One 2017). Intriguingly, recent studies showed that HIF-PHI administration in CKD mice reduced intact FGF23 levels (but still more C-terminal FGF23 fragments) by amelioration of kidney function and better iron utilization (Noonan ML et al. JBMR 2021; Hanudel MR et al. Kidney Int 2021). The latter needs to be taken into account as iron deficiency also results in increased production and cleavage of FGF23 (Farrow EG et al. PNAS 2011; Wolf M et al. JBMR 2013; Eisenga MF et al. JASN 2017). Hence, the different effects of ESA and HIF-PHI on FGF23 combined with the most likely better iron utilization should be discussed. Also, concerning the previously identified adverse outcomes seen with ESA administration aiming at normalization of hemoglobin levels in large RCTs (CHOIR/TREAT/CREATE), the induction of increased levels of cFGF23 as a potential mechanism for the detrimental effects of ESA therapy needs to be considered (Eisenga MF et al. J Am Heart Assoc 2019).

Mechanistically, FGF23 could also be crucially involved in several pathways linking HIF-PHI and iron utilization. For example, HIF-PHI administration results in more C-terminal FGF23 fragments, and since the amelioration of the anemia in CKD following HIF-PHI administration is ERFE-independent (Hanudel MR et al. Kidney Int 2021), it could be that the noted increase in C-terminal FGF23 fragments following HIF-PHI functions as a direct hepcidin suppressor. Recently, it has namely been shown that C-terminal FGF23 fragments decrease the BMP6/SMAD pathway, crucial for hepcidin secretion (Agoro R et al. Haematologica 2021). Hence, it could be that the C-terminal FGF23 fragments which ensue following HIF-PHI administration function as a direct BMP antagonist linking HIF-PHI and hepcidin suppression.

Another aspect that needs to be considered is the bidirectional nature of the relationship between EPO/HIF and FGF23. FGF23 is a crucial regulator of erythropoiesis where erythroid progenitor cells express FGF23 receptors and inhibition of iFGF23 increases early and late erythroid populations by decreasing erythroid cell apoptosis, leads to more renal and bone marrow HIF1α expression and subsequent EPO mRNA expression, resulting in higher EPO levels (Van Vuren A et al. Front Physiol 2019).
In conclusion, similar to the KDIGO Controversies Conference on Optimal Anemia Management in CKD, which took place in Barcelona 2019, where we discussed the effect of iron deficiency and the different IV iron compounds on FGF23, discussion regarding the impact of ESA and HIF-PHI, combined with the crosslink with iron homeostasis, on FGF23 homeostasis and vice versa merits attention.

James Fotheringham (University of Sheffield):
Please consider the cost-effectiveness or more specifically proposed cost-utility of these treatments. These technologies have been considered by ICER and are under evaluation by NICE. As written the scope focuses on cost-savings through these treatments, but it is permitted for these technologies to be more expensive if they yield additional quality-adjusted life years.

Chuan Ming Hao (Fudan University):
Cardiovascular safety (thrombosis): • patients: o NDD, DD, IDD, • dose of PHI (frequency of dosing), • speed of Hb correction, • iron… • benefits/risk o Cardiovascular concerns? o Cardiovascular advantages? Potential concerns: monitoring and biomarkers • Cancer • Retinopathy • Thrombotic events • Poly cystic kidney disease • Progression of CKD … How to use PHI • Which patients (ESA naïve, ESA switch) o CKD anemia o ESA hyporesponsive patients (how to switch?) o Inflammation/infection? o Oral • Assessment of response and Hb target • Iron status o Before PHI treatment, during PHI o Iron "repletion", parameters? Other effects • Lipid profile • Blood pressure • Metabolism • Immunity • …

Joanna Hudson (University of Tennessee Health Science Center - Clinical Pharmacist and Academician specializing in Nephrology):
The key issues and questions to be addressed regarding HIF-PHIs are comprehensive and relevant. I do see that this should be a multidisciplinary group and I would advocate for a nephrology clinical pharmacist to be part of this panel of individuals. I look forward to seeing the output from this group!

Kunitoshi Iseki (Okinawa Heart and Renal Association - OHRA, Former KDIGO ECM):
I have been waiting for this KDIGO CC and am really excited. There will be many research ideas for international collaboration from this CC. Although, compared to that od ACEI and ARB for hypertension, colleague’s responses are not yet great, as we have still the regulation of reimbursement.

We surveyed the use of HIF-PHI among our dialysis facilities in Okinawa, Japan (N=74). Among them, 38 units (51.4%) are using it, but other half don’t. Since the beginning of HIF-PHI on November 2019, we have now 5 drugs (roxodustat, daprodustat, vadadustat, enarodustat, and molidustat). Explanations for such situation are, 1) few number of ESA
resistance, 2) few of side-effects on DM retinopathy, malignancies, thrombosis, and 3) reimbursement issue. However, we have prominent responses among aplastic red-cell anemia patients.

**Ayman Karkar (Baxter AG):**

It would be of interest to listen to the latest on Anemia management in CKD.

**Rümeyza Kazancıoğlu (Bezmialem Vakif University):**

Thank you for this detailed scope of work. I have no other suggestions.

**Najib Khalife (Astellas Pharma Europe):**

1. What is the efficacy of HIF-PHIs in the treatment of anemia in patients with CKD not on dialysis therapy and the mean hemoglobin change that we can expect under standard treatment?

The efficacy of HIF-PHIs in the treatment of anemia in patients with CKD not on dialysis has been investigated in clinical trials but not yet available in Real World Evidence (with evaluation still ongoing in Japan and China). In a recent ERA-EDTA Free Communication [Nephrology Dialysis Transplantation. 2021. p. i50–1 [FC073] by Dimkovic N, Esposito C, Barratt J, et al.: Regional Efficacy and Safety Results of Roxadustat Compared with Placebo or Darbepoetin Alfa in Non-dialysis-dependent Chronic Kidney Disease Patients with Anaemia, the mean Hb change in g/dL from baseline (BL) to week 28-36 without rescue therapy was: 2.01 for roxadustat vs 0.37 in placebo control in Europe, 1.80 in roxadustat vs 0.21 in placebo in US, and 1.80 in roxadustat vs 0.06 in other regions. When comparing roxadustat to Darbepoetin alfa (DA), the mean Hb change in g/dL from BL was: 1.64 in roxadustat vs 1.75 in DA) control in Western EU and Israel, 1.94 in roxadustat vs 1.88 in DA control in Central and East Europe. Other published data from China and Japan showed similar efficacy In China, the mean Hb change from baseline to week 8 was 1.9 g/dL for roxadustat and -0.4 g/dL for placebo (Chen 2019). In Japan, the mean change of Hb from baseline to weeks 18-24 was 1.34 g/ dL (roxadustat 50 mg) and 1.30 g/dL (roxadustat 70 mg).

Secondary efficacy endpoints were investigated as possibly related to the mechanism of action and iron sparing characteristics of HIF-PHIs. In a recently published, peer-reviewed article by Barrett et al, entitled “Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: A phase 3, randomised, open-label, active-controlled study (DOLOMITES)”, few patients used IV iron during Weeks 1–36 (roxadustat: n = 20, 6.2%; DA: n = 37, 12.7%). In these patients, the mean (SD) monthly dose of IV iron during Weeks 1–36 was 34.74 (29.96) mg and 69.59 (67.34) mg in the roxadustat and DA groups, respectively. Concomitant use of oral preparations of bivalent (roxadustat: 43.7%; DA: 49.8%) and
trivalent (roxadustat: 35.3%; DA: 44.7%) iron was lower in roxadustat-treated patients. In this study, oral iron was required for either group for ferritin < 100 ng/mL or TSAT < 20%. IV iron was allowed in the roxadustat arm if there was an inadequate Hb response after at least 2 dose increases or the maximum dose limit was reached and with iron deficiency or intolerance to oral iron. In the DA group, IV iron was required if ferritin < 100 ng/mL or TSAT < 20%.”


2. What should the hemoglobin target be in relation to HIF-PHI use? Do higher hemoglobin levels remain an area for concern and should there still be an upper limit that is below normal?

3. What is the efficacy of HIF-PHI in the treatment of anemia in patients on dialysis therapy and the mean hemoglobin change that we can expect under standard treatment?

Comment: The efficacy of HIF-PHI in the treatment of anemia in patients with CKD on dialysis has been investigated in clinical trials but not yet available in Real World Evidence (with evaluation still ongoing in Japan and China). In a recently published article by Charytan et al entitled A Randomized Trial of Roxadustat in Anemia of Kidney Failure: SIERRAS Study, the mean baseline hemoglobin was 10.3 g/dl in both treatment groups. Mean (SD) changes in hemoglobin averaged over weeks 28 to 52 were 0.39 (0.93) and −0.09 (0.84) g/dl in roxadustat and epoetin alfa groups (least squares mean [LSM] difference: 0.48 [95% CI: 0.37, 0.59]; P < 0.001). Roxadustat was noninferior to epoetin alfa for hemoglobin maintenance. The percentage of patients with mean hemoglobin ≥10.0 g/dl averaged over weeks 28 to 52 was 66.1% (95% CI: 61.0, 70.9) and 58.6% (95% CI: 53.4, 63.7) in the roxadustat and epoetin alfa groups (responder rate difference: 7.6% [95% CI: 0.9, 14.3]). Patients with a hemoglobin response between 10.0–12.0 g/dl averaged over weeks 28 to 36 was 64.1% (95% CI: 58.7, 69.2) and 60.8% (95% CI: 55.5, 65.9) in the roxadustat and epoetin alfa groups (responder rate difference: 2.7% [95% CI: −4.3, 9.7]).

For both endpoints, roxadustat was noninferior to epoetin alfa, as the lower limits of the 95% CIs were above the prespecified margin of −15%. At baseline, the proportion of patients with hs-CRP level greater than ULN was slightly higher in the roxadustat versus epoetin alfa group. During 52 weeks of treatment with roxadustat, mean increases in hemoglobin levels were comparable between patients with baseline hs-CRP greater than ULN and hsCRP less than or equal to ULN with stable mean weekly dosing. By contrast, mean epoetin alfa dosing increased by ~30% during weeks 21 to 24 and ~60% during weeks 41 to 52. Patients with baseline hsCRP greater than ULN required larger increases in mean weekly epoetin alfa doses versus those with baseline hs-CRP ≤less than or equal to ULN.

Additional efficacy endpoints related to reduction of IV iron use and reduction in Hepcidin: the mean (SD) monthly i.v. iron use per patient-exposure month during weeks 28 to 52 was 17.1 (53.4) mg versus 37.0 (106.8) mg in the roxadustat versus epoetin alfa group (LSM difference: −20.1 [95% CI: −33.8, −6.45]; P <0.009). At baseline, mean (SD) hepcidin levels were 272.85 (129.70) and 270.67 (134.52) μg/L in the roxadustat and epoetin alfa groups.
By week 4, the mean (SD) change from baseline was $-19.70 \pm 130.19$ and $-0.45 \pm 128.7$ in the roxadustat and epoetin alfa group. This larger hepcidin reduction in the roxadustat group persisted through week 52, when mean (SD) changes from baseline were $-95.53 \pm 148.27$ and $-66.66 \pm 141.61$ (LSM difference: $-19.12 \pm 39.52$, 1.28; $P = 0.07$ [nominal]).

https://www.sciencedirect.com/science/article/pii/S2468024921010895?via%3Dihub In another published study by Provenzano et al. entitled: Roxadustat for anemia in patients with end-stage renal disease incident to dialysis, the intent-to-treat population included patients randomized to roxadustat ($n = 522$) or epoetin alfa ($n = 521$). Mean (standard deviation) Hb changes from baseline averaged over Weeks 28–52 were 2.57 (1.27) and 2.36 (1.21) in the roxadustat and epoetin alfa groups. Roxadustat was non-inferior [least squares mean difference: 0.18 (95% CI 0.08, 0.29)] to epoetin alfa. Percentages of patients with an Hb response were 88.2% and 84.4% in the roxadustat and epoetin alfa groups, respectively. Roxadustat was non-inferior to epoetin alfa [treatment-group difference 3.5% (95% CI −0.7%, 7.7%)].


4. Are there subgroups for which HIF-PHIs might be particularly beneficial, such as patients receiving home dialysis therapies?

Comment: patients receiving home dialysis and patients receiving peritoneal dialysis (PD) at home can potentially benefit from oral HIF-PHIs because it would reduce the need for hospital visits. Akizawa et al publication on Intermittent Oral Dosing of Roxadustat in Peritoneal Dialysis Chronic Kidney Disease Patients with Anemia: A Randomized, Phase 3, Multicenter, Open-Label Study, investigated the efficacy and safety of roxadustat in Japanese CKD patients with anemia on peritoneal dialysis (PD) who were previously treated or not treated with erythropoiesis stimulating agents (ESAs). Patients not previously receiving ESA (ESA-Naïve group) were randomized to roxadustat at a starting dose of 50 or 70 mg three times weekly; patients previously receiving ESA (ESA-Converted group) switched from ESA to roxadustat 70 or 100 mg three times weekly depending on the prior ESA dose. Outcomes included maintenance rate of average hemoglobin (Hb) level within 10–12 g/dL at weeks 18–24, cumulative response rate at end of treatment (Hb thresholds, 10.0 g/dL or 10.5 g/dL; Hb increase, ≥1.0 g/dL), and average Hb levels at weeks 18–24. Fifty-six patients were enrolled (ESA-Naïve, $n = 13$; ESA-Converted, $n = 43$). Maintenance rates (weeks 18–24) were 92.3% (95% CI: 64.0–99.8; ESA-Naïve) and 74.4% (95% CI: 58.8–86.5; ESA-Converted). Cumulative response rate was 100.0% in the ESA-Naïve group. Average Hb levels (weeks 18–24) were 11.05 g/dL (95% CI: 10.67–11.42; ESA-Naïve) and 10.93 g/dL (95% CI: 10.73–11.13; ESA-Converted). The mean (SD) baseline Hb levels were 9.35 g/dL.
(0.75) and 10.85 g/dL (0.54) in the ESA-Naïve and ESA-Converted groups, respectively. The mean change in average Hb levels from baseline to weeks 18–24 was 1.69 g/dL (95% CI: 1.06, 2.33) in the ESA-Naïve group, and 0.14 g/dL (95% CI: −0.12, 0.39) in the ESA-Converted group. https://onlinelibrary.wiley.com/doi/full/10.1111/1744-9987.12885

5. What are the currently available safety data surrounding the use of HIF-PHIs in different populations: patients not on dialysis; patients who are incident or prevalent to dialysis?

Comment: A recently published peer-reviewed article by Barrett et al on non dialysis patients showed that the safety profiles for roxadustat and Darbepoetin, used at doses required to achieve Hb 10–12 g/dL, were comparable. The HR (95% CI) for the composite endpoints MACE and MACE+ for both the safety-emergent period analysis [MACE: 0.81 (0.52–1.25), P = 0.339; MACE+: 0.90 (0.61–1.32), P = 0.583; and on-study analysis [MACE: 0.89 (0.60–1.33), P = 0.574; MACE+: 0.93 (0.65–1.32), P = 0.682; data showed favorable trends for roxadustat; however, these analyses were not sufficiently powered to demonstrate non-inferiority or superiority.

https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfab191/6291250?searchresult=1 Chen et al publication entitled: Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis, reported on the most frequent adverse event was upper respiratory infection, which occurred in 37 patients (18.1%) in the roxadustat group and in 11 (11.0%) in the epoetin alfa group. A total of 29 patients (14.2%) treated with roxadustat and 10 (10.0%) treated with epoetin alfa reported having at least one serious adverse event during treatment. The most frequently reported serious adverse event was vascular-access complication, which occurred in similar proportions of the treatment groups (6 patients [2.9%] in the roxadustat group and 3 patients [3.0%] in the epoetin alfa group). Vascular-access complications included the terms arteriovenous fistula occlusion, arteriovenous fistula site complication, and arteriovenous fistula thrombosis. No deaths occurred during the reporting period. Adverse events that occurred in at least 5% of the patients in either group were: Hyperkalemia was reported more frequently in the roxadustat group than in the epoetin alfa group in this open-label trial. On the basis of central laboratory assessments of blood samples obtained at baseline (week 1) and every 4 weeks, the mean changes in potassium level were as follows: at week 5, a change of 0.12 mmol per liter in the roxadustat group and 0.01 mmol per liter in the epoetin alfa group; at week 13, a change of −0.04 mmol per liter and −0.01 mmol per liter, respectively; and at week 21, a change of −0.07 mmol per liter and −0.02 mmol per liter, respectively. The proportion of patients with potassium values within categories from 5.5 mmol per liter or less, more than 5.5 to 6.0 mmol per liter, more than 6.0 to 6.5 mmol per liter, and more than 6.5 mmol per liter at baseline and at weeks 13 and 27 were generally similar in the treatment groups. https://www.nejm.org/doi/full/10.1056/nejmoa1901713
Said Khamis (Faculty of Medicine, Menoufia University Egypt):
We need more practical approach to the group of CKD patients having what is called naturally occurring high hemoglobin. Thanks

Arif Khwaja (Sheffield Kidney Institute):
Very comprehensive scoping document. I wasn't sure if you would cover this under safety but it would be good to ultimately get practical guidance on whether everyone needs a renal US within 3 months of starting these drugs. Also be interesting to review any evidence of efficacy in inflammatory states/epo-resistant states.

Pech Kimkoung (UHS):
Thanks you for your sharing this knowledge

José Lopes (Division of Nephrology, Centro Hospitalar Universitário Lisboa Norte):
No comments.

Iain Macdougall (King’s College Hospital, London, UK):
Generally an excellent Scope of Work document - congratulations to the author(s) who put this together! One thing that I think is missing is the question of whether or not there are differences between the various HIF-PHI preparations. The document as written suggests that they are all the same, and that the answers to the questions posed are generic, and this may or may not be the case. Personally, I feel the body of evidence suggests that there are significant differences between them, and to ignore this issue completely in the Consensus Conference I feel is misguided. Of course if KDIGO feels otherwise, then I can accept this, given that there may be commercial sensitivities with this question but I feel at least we need to give a reason for avoiding this issue if we choose so to do.

Sandip Mitra (Professor of Nephrology):
Important area for KDIGO work. I think reviewing current knowledge, state of art evidence in the setting of current practice is crucial. Anemia management has not fundamentally changed despite emerging new evidence. A KDIGO workshop would be able to tease out the quality of knowledge and an action agenda around practice change in anemia. I would be keen to contribute to discussion on the management of anemia and use of HIF-PHI in Dialysis modalities (Group 2) including Home dialysis modalities (my area of expertise) and specific issues around its management in clinical practice.

Takeshi Nakanishi (Sumiyoshigawa Hospital):
Each HIF stabilizer is a structural analog of 2-oxoglutarate (2-OG) that reversibly inhibit HIF-PHD which stimulate HIF responses in the presence of normal oxygen levels. HIF-PHD
is one of the 2-OG dependent dioxygenases which represent a conserved class of enzymes that catalyze the hydroxylation of proteins, nucleic acids, and metabolites. Members of this class are involved in diverse cellular processes including not only oxygen sensing but also DNA/RNA repair, the posttranslational modification of collagens and histones, and metabolism. Recently, 2-OG had been demonstrated to play several important roles in the pendrin-dependent Cl- absorption as well as the prevention of sarcopenia, aging, and osteoporosis. Each HIF stabilizer had been selected by assaying erythropoietin levels but might not be tested in diverse 2-OGDD functions. We should focus on diverse functions of HIF stabilizers, as 2-OG analogs, beyond the therapy for renal anemia.

Alberto Ortiz (Fundacion Jimenez Diaz University Hospital and research institute, Universidad Autonoma de Madrid):
Group 1, point 6. Vein preservation for HD access

Group 1, new point 8. What is the optimal rate of Hb correction when using HIF-PHls

Group 1, new point 9. What studies (e.g. length of follow-up) are needed to assess potential beneficial effects of HIF-PHls derived from improved lipid profiles.

Group 2, point 7. Are there specific safety concerns in patients who are hyporesponsive to ESA or iron?

Group 4. New point 9. What is the clinical impact of Thyroid Hormone Recepto activation by HIF-PHls such as roxadustat? Should thyroid hormones be monitored or is there any impact on the interpretation of thyroid hormone results?

Marlies Ostermann (Guy's & St Thomas Hospital London):
Congratulations on hosting a controversies meeting which addresses a very important topic. The scope covers all important aspects. My only comment would be that most questions refer to the chronic more stable situation. Would you consider adding a section on "implications during acute illness", ie should Hb targets be modified? Are the new drugs safe and effective or should they be stopped? Are there important interactions with drugs or specific acute comorbidities? Apart from this, the scope looks excellent.

Draško Pavlović (Polyclinic for Internal Medicine and Dialysis B.Braun Avitum):
HIF-PHIs for dialysis patients with malignant disease?

Cost benefit of HIF-PHIs vrs LSE

Emilio Rodrigo (University Hospital Marqués de Valdecilla/IDIVAL):
The scope of work about the KDIGO Controversies Conference on Novel Anemia Therapies in CKD is sound and comprehensive. All the questions in the 4 groups are relevant and worthy to review. I only miss a more practical view with two more questions (for both groups 1 and 2) that can be only partially answered with the current state of knowledge: 1- After an optimal iron replenishment, in which patients we should start with a HIF-PHIs instead of an ESA? In which patients are HIF-PHIs not recommended? In which patients may HIF-PHIs have some theoretically advantages? 2- In which patients could be beneficial a switching from an ESA to a HIF-PHIs? In which patients a switching from an ESA to a HIF-PHIs is contraindicated? The elaboration of an algorithm could help to optimize the prescription of HIF-PHIs. Relating to the pleiotropic effects beyond hemoglobin, we would suggest expanding the question 3 of group 4 analyzing the potential benefits of HIF-PHIs for treating (not only preventing) ischemia-reperfusion damage in kidney transplantation and stroke. Congratulations for this remarkable effort! Yours sincerely Emilio Rodrigo

**Simon Roger (Gosford Hospital, Australia):**
1. What is the efficacy of HIF-PHIs in the treatment of anemia in patients? we know that they work as protocol driven trials to correct or maintain Hb. why did some companies use non-traditional non-inferiority margins eg 1.0 vs 0.75g/dL

2. Is there any evidence that the use of HIF-PHIs slow down the progression of CKD, (in dialysis population)...copied and pasted, not relevant to dialysis

3. Do HIF-PHIs reduce iron requirements among patients receiving dialysis? raises the old question: is iron beneficial or detrimental to health?

4. Do we have safety data on patients who are simultaneously on ESA and HIF-PHI therapies? so will it be like type 2 diabetes, some oral hypoglycaemics to increase endogenous insulin (aka EPO) secretion and lower dose insulin (aka ESA)

**Guy Rostoker (Private Hospital Claude Galien, Quincy sous Sénart, France):**
Since HIF-Stabilizers (Duxstats) have been shown in non inferiority trials as efficacious as ASE , they could theoretically be used both in non-dialysis ESKD and dialysis ESKD instead. On the other hand, HIF-Stabilizers (Duxstats) seem of peculiar interest in inflammatory patients and those hypo-responsive to ESA. Finally, because trials of HIF-Stabilizers (Duxstats) have excluded patients suffering from immune mediated disease, auto and chronic inflammatory disease, patients who have had cancer and diabetics with proliferative retinopathy or ongoing atherosclerotic disease , phase IV trials or specific registers (with a careful prescription ) are warranted in these populations excluded of the trials for label.
Deepak Sharma (Ketav Kalp Healthcare & Research Private Limited):
Well considered and elaborated scope of work.

Narinder Singh (SGT University):
We were the first to demonstrate the role of Iron Dextran in Predialysis CKD way back in 2002 in Renal Failure

Mai Sugahara (The University of Tokyo Hospital):
The APSN and JSN both mention the importance of adequate iron supplementation in their recommendations on the appropriate use of HIF-PHI. The optimal strategies for iron supplementation, such as routes of administration, the optimal ferritin and TSAT levels during HIF-PHI treatment, may need to be discussed.

Mototsugu Tanaka (Niigata University Medical and Dental Hospital, Niigata, Japan):
Thank you for providing the Scope of Work documents. I do not have additional comments. The documents are well structured, and the questions are interesting. I am looking forward to make discussions on this document.

Yusuke Tsukamoto (Itabashi Chuo Medical Center):
I agree that this scope of coverage thoroughly cover the scope that we can discuss right now from the clinical point of view. I am sure the latest article by Kai and others give us an answer for one of the relevant caveats. N Engl J Med 2021;384:1601-12.

Pablo Urena (AURA Saint Ouen, Paris, France):
Group 4 should also discuss about other potential pleiotropic effects of PH inhibitors (PHI) on cartilage and bone cells. It is probably that in the long-term run PHI could negatively affect joint cartilages and positively bone mass. These could be potential areas of future research.
Milena Studer (Roche):

Comments on Group 1 and 2:
- On the role of EPO and iron in the era of HIFs: Are there differences among EPO preparations? Are there differences between short- or long-acting ESAs that should be considered?

Comments on Group 3/4:
- Safety profile of HIFs: ICER evidence report and FDA assessment of roxadustat data provides some interesting questions for discussion.

References for consideration:

**Recent reviews on ESAs and recent data from observational studies, with focus short- vs long-acting ESAs:**


**Recent data from observational studies and the PASS Roche sponsored study (already included and discussed in 2019 controversies conference):**

- Sakaguchi Y et al., Types of Erythropoietin-Stimulating Agents and Mortality among Patients Undergoing Hemodialysis, *JASN 30: 1037–1048, 2019.* (for interpretation of results please also check Locatelli CJASN 2019)

**Reports from ICER and FDA CV Advisory Committee on Roxadustat**

- FDA Briefing Document Cardiovascular and Renal Drugs Advisory Committee Meeting July 15, 2021 Roxadustat, [link].
July 01, 2021

FAO: Drs. Elaine Ku (University of California San Francisco, San Francisco, CA, USA) & David C. Wheeler (Centre for Nephrology, University College London, London, UK)

RE: AstraZeneca’s response to KDIGO’s call to action for comments on ‘KDIGO Controversies Conference on Novel Anemia Therapies in CKD - Scope of Work’

Dear Dr Ku & Dr Wheeler,

In response to KDIGO’s invitation for feedback on the Scope of Work for the upcoming KDIGO Controversies Conference on Novel Anemia Therapies in CKD, to be held in Berlin in December, we would like to share our comments on behalf of AstraZeneca. The scope of work appears very comprehensive and we look forward to participating in this important conference.

As a reminder, at the request of KDIGO, we have made all relevant literature to the development of roxadustat available to you in this folder: https://az.box.com/s/l3zwskhlevbe1gce9zrra7qv8p10gt73. The information may contain scientific information regarding investigational use of our products or information that is not found in current approved labeling. The enclosed information is intended to provide pertinent data regarding AstraZeneca products and should in no way be construed as a recommendation for the use of our products in any manner other than as approved and described in the labeling information. Prescribing information for approved AstraZeneca products may be obtained by visiting the AstraZeneca websites of the applicable country or region.

In regard to the Controversies Conference on Novel Anemia Therapies in CKD - Scope of Work, we would like to make the following minor suggestions:

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<td>CONFERENCE OVERVIEW. Sentence “One key question this conference will address is whether there is a specific population in which HIF-PHI should be preferred or avoided.”</td>
<td>We feel this could be interpreted as leading. A suggestion is to consider is “One key question this conference will address is the role HIF-PHI inhibitors will play in the management of anemia in patients with CKD”</td>
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<td><strong>Group 1: Therapeutic use of HIF-PHIs vs. current therapies in anemia management:</strong> CKD patients not on dialysis treatment; Bullet 4: Is there any evidence that the use of HIF-PHIs slow down the progression of CKD, improve cardiovascular endpoints (MACE) or physical function and health-related quality of life compared with iron/ESAs?</td>
<td>We would like to ensure that the delegates consider all clinically relevant endpoints to patients not on dialysis, such as avoidance of red blood cell transfusions and the associated consequences e.g. alloimmunization, transfusion reactions etc.; effects on iron parameters, hepcidin, need for iron replacement, health-care resource utilization, patient convenience &amp; independence</td>
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<td><strong>Group 2: Therapeutic use of HIF-PHIs vs. current therapies in anemia management:</strong> CKD patients treated with dialysis (patients incident and prevalent to dialysis); Bullet 4: Is there any evidence that the use of HIF-PHIs slow down the progression of CKD, improve cardiovascular endpoints (MACE) or physical function and health-related quality of life compared with iron/ESAs? Are there any differences between the incident vs prevalent dialysis populations?</td>
<td>We would like to ensure that the delegates consider all clinically relevant endpoints to dialysis patients, such as avoidance of red blood cell transfusions and the associated consequences e.g. alloimmunization, transfusion reactions etc.; effects on iron parameters, hepcidin, need for iron replacement, health-care resource utilization, patient convenience &amp; independence</td>
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<td><strong>Group 3: Safety profile of HIF-PHIs in CKD anemia management;</strong> Bullet 4: Are there theoretical or known safety differences between various HIF-PHI agents that are available or being developed in phase II/III trials?</td>
<td>We would like to suggest that you consider commenting on pharmacokinetic and pharmacodynamic differences between available HIF-PH inhibitors e.g. reversible vs irreversible inhibition of prolyl hydroxylase enzymes, relative inhibition of PHD isoforms, half-life etc.</td>
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<td><strong>Group 4: Pathophysiology of HIF-PHIs and pleiotropic effects beyond hemoglobin;</strong> Bullet 5: What are the benefits, risks, and differences of the current ESAs that are available (short-acting, long-acting [CERA], biosimilars/biogenerics)? How may or may not HIF-PHIs address the shortcomings of ESAs?</td>
<td>We would like to suggest this is a very extensive topic in its own right and may warrant a dedicated discussion group.</td>
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If you have any questions regarding the comments, please contact AstraZeneca Medical Information at 1-877-893-1510.

Yours sincerely,

Dr. Nisha Bhatt, MD
Executive Director, Medical Biopharmaceuticals
AstraZeneca
July 9, 2021

Dear KDIGO Committee Members:

Please accept this correspondence as an update to Rockwell Medical’s formal executive summary response to KDIGO on November 11, 2019.

Triferic and macromolecular intravenous (IV) iron are fundamentally different means of delivering iron into the body and, as such, we believe serve very different purposes in anemia management. Triferic is a small water-soluble iron salt that does not exceed the iron binding capacity of transferrin and thus, unlike macromolecular IV iron, does not need to be absorbed by the reticuloendothelial system and thus bypasses the liver. In other words, because Triferic does not exceed the total iron binding capacity of the blood, it avoids inflammatory, hepcidin-induced iron sequestration. Triferic is the first and only FDA-approved product indicated to replace iron and maintain hemoglobin in adult hemodialysis-dependent CKD patients.

As a KDIGO sponsor, we are pleased to be able to provide materials for consideration by the group and understand that these will be made available to the participants. We appreciate the opportunity to share relevant literature and data to be considered during the conference with KDIGO Management.

Please see the following bibliography for research publications associated with Triferic.

Best regards,

Marc L Hoffman, M.D.
Chief Medical Officer

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mhoffman@rockwellmed.com
www.rockwellmed.com
www.triferic.com
Bibliography – Ferric Pyrophosphate Citrate

(2006). Ferric Pyrophosphate Citrate. Drugs and Lactation Database (LactMed). Bethesda (MD). No information is available on the use of ferric pyrophosphate citrate during breastfeeding and the manufacturer recommends that it not be used during breastfeeding. An alternate intravenous drug with more published data available may be preferred. Pasteurization of milk by the Holder method reduces the concentration of iron in milk by about 6.5%.[1]


PURPOSE: The objective of this short review is to evaluate the efficacy of ferric pyrophosphate citrate and to determine its place in therapy based on the current published literature. METHODS: A literature search was conducted and pared down to yield 4 placebo controlled Phase II and III clinically relevant trials. FINDINGS: Ferric pyrophosphate citrate is a new intradialytic iron supplementation product that has been found to reduce the dose of erythropoiesis-stimulating agents and intravenous iron supplementation and to increase serum ferritin concentrations. IMPLICATIONS: This agent may be administered to patients with stage 5 chronic kidney disease receiving hemodialysis as a new iron supplementation option to maintain hemoglobin, transferrin saturation, and ferritin concentrations.


The purpose of this study is to evaluate the financial benefit and savings for this institution with the use of FPC and its effect on lowering the dose/use of ESAs and IV iron products. The same 100 patients were followed before and after the implementation of FPC in their dialysis treatment. In these 100 patients, the relative reduction in the average weekly dose of ESA was 26.4% and an absolute reduction of 14 mcg per week (~53 mcg vs. ~39 mcg; P<0.0001). Also, the total use of IV iron replacement therapy for the same 100 patients decreased. The relative reduction in total iron sucrose used was ~65.7% (30,337.6 mg vs. 10,400 mg), and the relative reduction in total sodium ferric gluconate used was ~98.2% (303,680.6 mg vs. 5100 mg).

CONCLUSIONS: FPC use in an outpatient dialysis center is associated with the reduction of ESAs and IV iron product usages. With the decreased use of these agents due to FPC’s implementation, the institution was able to realize a net savings of $296,751.49 in one fiscal year.


Dialysis patients have absolute and functional iron deficiencies. Traditionally, oral iron preparations have been insufficient to maintain iron stores to support erythropoiesis, especially in the setting of the ubiquitous use of erythropoiesis-stimulating agents. This has led to the widespread adoption of intravenous iron protocols designed to maintain iron stores at levels that are much higher than for patients not on dialysis. These protocols are often developed by dialysis providers and may be largely independent of the treating
nephrologist. Concerns about multiple risks associated with the use of intravenous iron persist. Despite this, mean ferritin levels in the United States have risen, partly due to more intravenous iron use and partly due to reduced erythropoiesis-stimulating agent use. Questions about the relationship of intravenous iron to infection, cardiac, and hepatobiliary risks remain. The failure of oral iron preparations to maintain iron stores continues to prompt the use of intravenous iron. Recently, studies with oral ferric citrate as a phosphate binder have shown improved iron stores and maintenance of hemoglobin, and studies with soluble ferric pyrophosphate added to dialysate have shown both maintenance of iron stores and hemoglobin. With new iron options that affect iron stores in dialysis patients, the use of intravenous iron and its potential risks may wane.


Treatment of anemia remains an integral component in the care of patients with end stage kidney disease receiving dialysis. Currently, both erythropoiesis stimulating agents and iron replacement agents remain important anemia management strategies for patients undergoing hemodialysis (HD). Ferric pyrophosphate citrate (FPC) was approved by the U.S. Food and Drug Administration in January 2015 as an iron replacement product in adult patients receiving long-term maintenance HD. FPC is administered to patients on HD through the dialysate.

Multicenter randomized, placebo-controlled phase three clinical studies (CRUISE 1 and 2) have found dialysate FPC to maintain hemoglobin level and iron balance in patients receiving chronic HD. Adverse events were similar in both the dialysate FPC-treated and placebo groups. Another study showed a significant reduction in the prescribed erythropoietin-stimulating agents dose at the end of treatment in the dialysate FPC-treated group compared with placebo. These studies have shown that dialysate FPC is efficacious and well tolerated. In this article, we review clinical studies evaluating the efficacy and safety of FPC and also propose a protocol for iron replacement in HD units where dialysate FPC is to be used.


BACKGROUND: Administration of ferric pyrophosphate citrate (FPC, Triferic) via hemodialysate may allow replacement of ongoing uremic and hemodialysis-related iron losses. FPC donates iron directly to transferrin, bypassing the reticuloendothelial system and avoiding iron sequestration. METHODS: Two identical Phase 3, randomized, placebo-controlled trials (CRUISE 1 and 2) were conducted in 599 iron-replete chronic hemodialysis patients. Patients were dialyzed with dialysate containing 2 microM FPC-iron or standard dialysate (placebo) for up to 48 weeks. Oral or intravenous iron supplementation was prohibited, and doses of erythropoiesis-stimulating agents were held constant. The primary efficacy end point was the change in hemoglobin (Hgb) concentration from baseline to end of treatment (EoT). Secondary end points included reticulocyte hemoglobin content (Chr) and serum ferritin. RESULTS: In both trials, Hgb concentration was maintained from baseline to EoT in the FPC group but decreased by 0.4 g/dL in the placebo group (P < 0.001, combined results; 95% confidence interval [CI] 0.2-0.6). Placebo treatment resulted in significantly larger mean decreases from baseline in Chr
(-0.9 pg versus -0.4 pg, P < 0.001) and serum ferritin (-133.1 microg/L versus -69.7 microg/L, P < 0.001) than FPC treatment. The proportions of patients with adverse and serious adverse events were similar in both treatment groups. CONCLUSIONS: FPC delivered via dialysate during hemodialysis replaces iron losses, maintains Hgb concentrations, does not increase iron stores and exhibits a safety profile similar to placebo. FPC administered by hemodialysis via dialysate represents a paradigm shift in delivering maintenance iron therapy to hemodialysis patients.

BACKGROUND: Soluble iron salts are toxic for parenteral administration because free iron catalyzes free radical generation. Pyrophosphate strongly complexes iron and enhances iron transport between transferrin, ferritin, and tissues. Hemodialysis patients need iron to replenish ongoing losses. We evaluated the short-term safety and efficacy of infusing soluble ferric pyrophosphate by dialysate. METHODS: Maintenance hemodialysis patients receiving erythropoietin were stabilized on regular doses of intravenous (i.v.) iron dextran after oral iron supplements were discontinued. During the treatment phase, 10 patients received ferric pyrophosphate via hemodialysis as monthly dialysate iron concentrations were progressively increased from 2, 4, 8, to 12 micrograms/dl and were then sustained for two additional months at 12 micrograms/dl (dialysate iron group); 11 control patients were continued on i.v. iron dextran (i.v. iron group). RESULTS: Hemoglobin, serum iron parameters, and the erythropoietin dose did not change significantly from month 0 to month 6, both within and between the two groups. The weekly dose of i.v. iron (mean +/- SD) needed to maintain iron balance during month 6 was 56 +/- 37 mg in the i.v. iron group compared with 10 +/- 23 mg in the dialysate iron group (P = 0.001). Intravenous iron was required by all 11 patients in the i.v. iron group compared with only 2 of the 10 patients receiving 12 micrograms/dl dialysate iron. The incidence of adverse effects was similar in both groups. CONCLUSIONS: Slow infusion of soluble iron pyrophosphate by hemodialysis may be a safe and effective alternative to the i.v. administration of colloidal iron dextran in maintenance hemodialysis patients.

Ferric pyrophosphate citrate (FPC) is a water-soluble iron salt administered via dialysate to supply iron directly to transferrin. The PRIME study tested whether treatment with FPC could reduce prescribed erythropoiesis-stimulating agent (ESA) use and maintain hemoglobin in hemodialysis patients. This 9-month, randomized, placebo-controlled, double-blind, multicenter clinical study included 103 patients undergoing hemodialysis 3-4 times weekly. The FPC group received dialysate containing 2 mumol/l of iron. The placebo group received standard dialysate. A blinded central anemia management group facilitated ESA dose adjustments. Intravenous iron was administered according to the approved indication when ferritin levels fell below 200 mug l. The primary end point was the percentage change from baseline in prescribed ESA dose at end of treatment. Secondary end points included intravenous iron use and safety. At the end of treatment, there was a significant 35% reduction in prescribed ESA dose in FPC-treated patients compared with placebo. The FPC patients used 51% less intravenous iron than placebo. Adverse and serious adverse events were similar in both groups. Thus, FPC
delivered via dialysate significantly reduces the prescribed ESA dose and the amount of intravenous iron needed to maintain hemoglobin in chronic hemodialysis patients.


Iron deficiency is a significant health problem across the world. While many patients benefit from oral iron supplements, some, including those on hemodialysis require intravenous iron therapy to maintain adequate iron levels. Until recently, all iron compounds suitable for parenteral administration were colloidal iron-carbohydrate conjugates that require uptake and processing by macrophages. These compounds are associated with variable risk of anaphylaxis, oxidative stress, and inflammation, depending on their physicochemical characteristics. Ferric pyrophosphate citrate (FPC) is a novel iron compound that was approved for parenteral administration by US Food and Drug Administration in 2015. Here we report the physicochemical characteristics of FPC. FPC is a noncolloidal, highly water soluble, complex iron salt that does not contain a carbohydrate moiety. X-ray absorption spectroscopy data indicate that FPC consists of iron (III) complexed with one pyrophosphate and two citrate molecules in the solid state. This structure is preserved in solution and stable for several months, rendering it suitable for pharmaceutical applications in solid or solution state.


FPC reduced the need for supplemental intravenous iron use by an average of 74% over the 2-year observation period and reduced the amount of erythropoietin-stimulating agents needed to maintain hemoglobin levels within the target range of 10.0 to 11.0 g/dL. Small mean improvements in quality of life were observed, as assessed by the 36-item Kidney Disease Quality of Life Questionnaire (KDQoL-36™) mental and physical component scores. As compared with US Renal Data System (USRDS) data, all-cause hospitalizations, infection-related hospitalizations, and deaths were reduced by approximately 50% after initiation of FPC.


Anemia affects millions of patients with chronic kidney disease (CKD) and prompt iron supplementation can lead to reductions in the required dose of erythropoiesis-stimulating agents, thereby reducing medical costs. Oral and intravenous (IV) traditional iron preparations are considered far from ideal, primarily due to gastrointestinal intolerance and the potential risk of infusion reactions, respectively. Fortunately, the emergence of novel iron replacement therapies has engendered a paradigm shift in the treatment of iron deficiency anemia in patients with CKD. For example, oral ferric citrate is an efficacious and safe phosphate binder that increases iron stores to maintain hemoglobin levels. Additional benefits include reductions in fibroblast growth factor 23 levels and the activation of 1,25 dihydroxyvitamin D. The new- generation IV iron preparations ferumoxyt, iron isomaltoside 1000, and ferric carboxymaltose are characterized by a reduced risk of infusion reactions and are clinically well tolerated as a rapid high-dose infusion. In patients undergoing hemodialysis (HD), ferric pyrophosphate...
citrate (FPC) administered through dialysate enables the replacement of ongoing uremic and HD-related iron loss. FPC transports iron directly to transferrin, bypassing the reticuloendothelial system and avoiding iron sequestration. Moreover, this paper summarizes recent advancements of hypoxia-inducible factor prolyl hydroxylase inhibitors and future perspectives in renal anemia management.


Gupta et al. describe a novel strategy for iron administration to hemodialysis patients, giving ferric pyrophosphate citrate via the dialysate. PRIME, a randomized controlled study comparing this technology against placebo, shows a 35% reduction in prescribed erythropoiesis-stimulating agent dose. The findings may be explained in part by a restrictive protocol for intravenous iron administration in the placebo group, producing lower ferritin levels. There were no obvious safety concerns. The general applicability of this technology, and its cost-effectiveness, are unclear at the present time.


There are several options available for intravenous application of iron supplements, but they all have a similar structure: an iron core surrounded by a carbohydrate coating. These nanoparticles require processing by the reticuloendothelial system to release iron, which is subsequently picked up by the iron-binding protein transferrin and distributed throughout the body, with most of the iron supplied to the bone marrow. This process risks exposing cells and tissues to free iron, which is potentially toxic due to its high redox activity. A new parenteral iron formulation, ferric pyrophosphate citrate (FPC), has a novel structure that differs from conventional intravenous iron formulations, consisting of an iron atom complexed to one pyrophosphate and two citrate anions. In this study, we show that FPC can directly transfer iron to apo-transferrin. Kinetic analyses reveal that FPC donates iron to apo-transferrin with fast binding kinetics. In addition, the crystal structure of transferrin bound to FPC shows that FPC can donate iron to both iron-binding sites found within the transferrin structure. Examination of the iron-binding sites demonstrates that the iron atoms in both sites are fully encapsulated, forming bonds with amino acid side chains in the protein as well as pyrophosphate and carbonate anions. Taken together, these data demonstrate that, unlike intravenous iron formulations, FPC can directly and rapidly donate iron to transferrin in a manner that does not expose cells and tissues to the damaging effects of free, redox-active iron.


BACKGROUND: Iron deficiency is a common cause of anemia in pediatric patients with hemodialysis-dependent chronic kidney disease (CKD-5HD). Ferric pyrophosphate citrate (FPC, Triferic(R)) donates iron directly to transferrin, bypassing the reticuloendothelial system and avoiding iron sequestration. Administration of FPC via dialysate or intravenously (IV) may provide a suitable therapeutic option to current IV iron preparations for these patients.
METHODS: The pharmacokinetics and safety of FPC administered via dialysate and IV to patients aged < 6 years (n = 3), 6 to < 12 years (n = 4), and 12 to < 18 years (n = 15) were investigated in a multicenter, open-label, two-period, single-dose study. FPC (0.07 mg iron/kg) was infused IV into the venous blood return line during hemodialysis session no. 1. FPC iron was added to bicarbonate concentrate to deliver 2 μM (110 μg/L) iron via dialysate during hemodialysis session no. 2. RESULTS: Mean serum total iron concentrations peaked 3 to 4 h after administration via dialysate and 2 to 4 h after IV administration and returned to baseline by 10 h after the start of hemodialysis for both routes. Iron exposure was greater after administration via dialysate than after IV administration. The absolute amount of absorbed iron after administration via dialysate roughly doubled with increasing age, but the weight-normalized amount of absorbed iron was relatively constant across age groups (~0.06–0.10 mg/kg). FPC was well tolerated in the small number of patients studied. CONCLUSIONS: FPC iron can be administered to pediatric patients with CKD-SHD via dialysate or by the IV route. Further study of FPC administered to maintain hemoglobin concentration is indicated.


Ferric pyrophosphate citrate (Triferic) is a water-soluble iron salt that is administered via dialysate to maintain iron balance and hemoglobin in hemodialysis patients. This double-blind, randomized, placebo-controlled, single-, ascending-dose study was conducted to evaluate the pharmacokinetics and safety of intravenous ferric pyrophosphate citrate in 48 healthy iron-replete subjects (drug, n = 36; placebo, n = 12). Single doses of 2.5, 5.0, 7.5, or 10 mg of ferric pyrophosphate citrate or placebo were administered over 4 hours, and single doses of 15 or 20 mg of ferric pyrophosphate citrate or placebo were administered over 12 hours via intravenous infusion. Serum total iron (sFetot), transferrin-bound iron (TBI), hepcidin-25, and biomarkers of oxidative stress and inflammation were determined using validated assays. Marked diurnal variation in sFetot was observed in placebo-treated subjects. Concentrations of sFetot and TBI increased rapidly after drug administration, with maximum serum concentrations (Cmax) reached at the end of infusion. Increases in baseline-corrected Cmax and area under the concentration-time curve from 0 to the time of the last quantifiable concentration (AUC0-t) were dose proportional up to 100% transferrin saturation. Iron was rapidly cleared (apparent terminal phase half-life 1.2–2 hours). No significant changes from baseline in serum hepcidin-25 concentration were observed at end of infusion for any dose. Biomarkers of oxidative stress and inflammation were unaffected. Intravenous doses of ferric pyrophosphate citrate were well tolerated. These results demonstrate that intravenous ferric pyrophosphate citrate is rapidly bound to transferrin and cleared from the circulation without increasing serum hepcidin levels or biomarkers of oxidative stress or inflammation.


Management of anemia remains an integral component in the care of patients with chronic kidney disease undergoing hemodialysis. In addition to erythropoiesis-stimulating agents, iron-replacement agents remain a key strategy for anemia treatment in this patient population. Ferric pyrophosphate citrate (FPC), a novel iron-replacement agent, was approved by the US
Food and Drug Administration in January 2015 for use in adult patients receiving chronic hemodialysis (HD). This iron product is administered to patients on HD via the dialysate. The recently published, multicenter, randomized, placebo-controlled, phase 3 clinical trials found FPC to maintain hemoglobin level and iron balance in patients undergoing chronic HD. The mean hemoglobin level in these phase 3 clinical studies was maintained from baseline to the end of the treatment in the dialysate iron (FPC-treated) group, however, it decreased by 0.4 g dL in the control group (P < 0.001). Adverse and serious adverse events were similar in both groups. Another recent study showed a significant reduction in the prescribed ESA dose at the end of treatment in the FPC-treated group compared with placebo. These studies have shown that FPC administered via the dialysate is efficacious and apparently well tolerated. In this article, in addition to reviewing the clinical studies evaluating the efficacy and safety of FPC, we propose a protocol for iron management in HD centers where FPC is to be used.


End-stage renal disease results in anemia caused by shortened erythrocyte survival, erythropoietin deficiency, hepcidin-mediated impairment of intestinal absorption and iron release, recurrent blood loss, and impaired responsiveness to erythropoiesis-stimulating agents (ESAs). Iron malabsorption renders oral iron products generally ineffective, and intravenous (IV) iron supplementation is required in most patients receiving maintenance hemodialysis (HD). IV iron is administered at doses far exceeding normal intestinal iron absorption. Moreover, by bypassing physiologic safeguards, indiscriminate use of IV iron overwhelms transferrin, imposing stress on the reticuloendothelial system that can have long-term adverse consequences. Unlike conventional oral iron preparations, ferric citrate has recently been shown to be effective in increasing serum ferritin, hemoglobin, and transferrin saturation values while significantly reducing IV iron and ESA requirements in patients treated with HD. Ferric pyrophosphate citrate is a novel iron salt delivered by dialysate; by directly reaching transferrin, it obviates the need for storing administered iron and increases transferrin saturation without increasing serum ferritin levels. Ferric pyrophosphate citrate trials have demonstrated effective iron delivery and stable hemoglobin levels with significant reductions in ESA and IV iron requirements. To date, the long-term safety of using these routes of iron administration in patients receiving HD has not been compared to IV iron and therefore awaits future investigations.